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Original article

Measuring fatigue with multiple instruments in a Brazilian cohort of early rheumatoid arthritis patients

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ABSTRACT

Objective: To assess the prevalence of fatigue in a Brazilian population with early rheumatoid arthritis using multiple instruments, and the predictors of these instruments by differents independent variables.

Methods: Cross-sectional study with direct interview and medical records review. Fatigue, dependent variable, was assessed using eight instruments: Profile of Mood States (POMS), Multidimensional Assessment of Fatigue scale (MAF), Fatigue Severity Scale (FSS), Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ), Numerical Rating Scales (BRAF-NRS), Short-form Survey 36 (SF-36), Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) and Visual Analogic Scale for Fatigue (VASf). Independent variables: sociodemographic, clinical and serological, were measured using medical records and direct interview. Disability and disease activity were assessed using the Health Assessment Questionnaire (HAQ) and disease activity assessed using the Disease Activity Score 28 joints (DAS28). The scores of scales demonstrated the level of fatigue and multiple linear regression method used in statistical analysis to demonstrate prediction models.

Results: A total of 80 patients was assessed, and 57 reported clinically relevant fatigue (VASf > 2), representing 71.25% prevalence point (51 women [89.5%], mean age 48.35 ± 15 years, and mean disease duration of 4.92 ± 3.8 years). Eight predictive models showed statistical significance, one for each fatigue instrument. The highest coefficient of determination (R^2) was 56% for SF-36 and the lowest (R^2 = 21%) for FSS. The HAQ was the only independent variable to predict fatigue on all instruments.

Conclusion: Clinically relevant fatigue is a highly prevalent symptom and is mostly predicted by disability and age in the population assessed.

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Mensuração da fadiga com múltiplos instrumentos em uma coorte brasileira de pacientes com artrite reumatoide em fase inicial

Palavras-chave:
Incapacidade
Fadiga
Artrite reumatoide

RESUMO

Objetivo: Avaliar a prevalência de fadiga em uma coorte brasileira de pacientes com artrite reumatoide em fase inicial com múltiplos instrumentos e os preditores desses instrumentos de acordo com diferentes variáveis independentes.

Métodos: Estudo transversal com entrevista direta e revisão de prontuários. A fadiga, a variável dependente, foi avaliada por meio de oito instrumentos: *Profile of Mood States* (POMS), *Multidimensional Assessment of Fatigue Scale* (MAF), *Fatigue Severity Scale* (FSS), *Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire* (BRAF-MDQ), *Numerical Rating Scales* (BRAF-NRS), *Short-form Survey 36* (SF-36), *Functional Assessment of Chronic Illness Therapy Fatigue Scale* (Facit-F) e Escala Visual Analógica de fadiga (VASf). Variáveis independentes: mensuraram-se dados sociodemográficos, clínicos e sorológicos por meio da análise de prontuários e entrevista direta. A incapacidade e a atividade da doença foram avaliadas com o *Health Assessment Questionnaire* (HAQ). A atividade da doença foi avaliada com o *Disease Activity Score 28 joints* (DAS-28). As pontuações das escalas mostraram o nível de fadiga e usou-se o método de regressão linear múltipla na análise estatística para demonstrar os modelos de predição.

Resultados: Avaliaram-se 80 pacientes; 57 relataram fadiga clinicamente relevante (VASf > 2), representaram uma prevalência de 71,25% (51 mulheres [89,5%], média de 48,35 ± 15 anos e duração média da doença de 4,92 ± 3,8 anos). Oito modelos preditivos mostraram significância estatística, um para cada instrumento de fadiga. O maior coeficiente de determinação (R^2) foi de 56% para o SF-36 e o menor (R^2 = 21%) foi para a FSS. O HAQ foi a única variável independente que predisse a fadiga em todos os instrumentos.

Conclusão: A fadiga clinicamente relevante é um sintoma altamente prevalente e é principalmente predita pela incapacidade e idade na população avaliada.

Introduction

Rheumatoid Arthritis (RA) is an autoimmune, chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of the synovial joints that could lead to severe disability and premature mortality.[1] RA affects between 0.5% and 1% of the general population and the impact on an individual's functional capacity results in a great economic burden to the individual and to society. It is estimated that 1.3 million individuals suffer from the disease in Brazil. Early RA is defined as the diagnosis given in the first weeks or months, usually less than 06 months, of joint symptoms or signs.[1,2]

Fatigue has grown in importance among patients with chronic diseases, despite of pain being a prevalent symptom. Fatigue is the enduring sensation of weakness, lack of energy, tiredness or exhaustion, and is reported by 40–80% of RA patients as their most disabling symptom. In addition, fatigue is not related to overexertion and is poorly relieved by rest; it is often multifactorial and prone to worsening by disease-related components, such as comorbid conditions, disease duration and/or activity, functional status, lifestyle factors, level of activity and inadequate social support.[3–5]

Studies have been conducted over the last 10–15 years to identify the characteristics of fatigue, its predictors, its effects, the correlation with several aspects of the disease, as well as the development of new scales to measure fatigue, involving various domains. With respect to fatigue predictors and associated factors, only the study of Bianchi et al. assessed the correlation between fatigue and clinical and psychological variables. By using the Fatigue Assessment of Chronic Illness Therapy (FACIT-F), they observed that fatigue is an independent parameter, probably more related to psychological and functional impairments. They considered all RA patients, i.e., patients with early and established RA.[6]

According to Dupond, psychological fatigue or weariness is the most common pattern of fatigue, varying from 20% to 70% in RA patients, and that depression is the main source of fatigue in classic inflammatory rheumatic diseases.[7] Minnock et al. conducted a longitudinal study with RA patients (n = 87) to assess the correlation of fatigue and disease activity. They observed that fatigue is not explained by disease activity as represented by the ACR core set outcomes, but is a behavioral variable with multifactorial influences, that vary with time of disease.[8]

Considering that fatigue predictors and associated factors are poorly investigated, or led to inconclusive directions, it is necessary to consider a study whose findings could predict fatigue across multiple independent variables. Furthermore, the use of patient-reported outcome measures (PROMs) assessing several domains may point out how fatigue affects each individual. In addition, studies drawing an early RA patient profile may also help develop more

efficient approaches and public policies for rheumatoid arthritis.

Therefore, the aim of this study was to assess fatigue in a Brazilian population with early RA, using all the instruments available in Portuguese and assess the prediction models for fatigue by disease activity, disability, sociodemographic, clinical and serological variables.

Material and methods

Design

This is a cross-sectional study, carried out between May 2014 and May 2015, involving direct interview and review of the medical records of the patients diagnosed with early RA. This study was approved by the relevant ethics committee (University of Brasília, School of Medicine, #897.320) and all patients signed a consent form.

Patients

The researchers assessed the patients of the Brazilian cohort of RA, an incident cohort of patients with early RA, and followed up in the Outpatient Rheumatology Clinic of the University Hospital of Brasília – University of Brasília.[7]

The inclusion criteria for this cohort comprises the following: early RA defined as the occurrence of articular symptoms, pain and edema with inflammatory pattern, associated or not with morning stiffness or other manifestations suggesting inflammatory joint disease (assessed by a single observer); at diagnosis, the disease duration more than 6 weeks, but less than 12 months, regardless of failure to meet the American College of Rheumatology (ACR) criteria.[9]

All selected patients retrospectively met the 2010 EULAR/ACR criteria.[1] The patients admitted to this cohort are prospectively followed from the moment of diagnosis and receive the standard treatment regimen used in the service, including synthetic or biological disease-modifying anti-rheumatic drugs (DMARDs), according to their needs. Currently, there are patients with 11 years of follow up from initial diagnosis.

Exclusion criteria

Juvenile idiopathic arthritis, pregnancy and previously established diagnosis of any other collagenous diseases.

Data collection

The researchers collected information on gender, age, ethnicity, years of study, family income, marital status, number of dependents, disease duration and morning stiffness. Functional status was assessed using the Health Assessment Questionnaire (HAQ).[10] Disease activity was assessed using the Disease Activity Score in 28 joints (DAS28)[11] and pain was assessed using the global pain Visual Analog Scale (VAS_P).

Smoking habits, the number of comorbidities (fibromyalgia, systemic arterial hypertension, dyslipidemia, diabetes mellitus, depression, hypothyroidism) and the number of extra-articular symptoms, morning stiffness, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were recorded. The researchers also assessed Swollen Joint Count in 28 joints (SJC28) and tender joint count in 28 joints (TJC28), body mass index (BMI), and collected subjective information on patients' mobility, daily living activities and pain/indisposition, age, ethnics, monthly income, years of study and marital status.

Fatigue assessment

The Profile of Mood States Fatigue/Inertia subscale ($POMS_F$) is part of the POMS questionnaire, designed to measure mood states and their variation in psychiatric patients, but currently is used in several other conditions. It contains 7 items that range from 0 (not at all) to 4 (extremely) to form a fatigue score from 0 to 28. Higher scores imply greater fatigue.[12]

The Multidimensional Assessment of Fatigue Scale (MAF) was developed to measure multiple dimensions of fatigue in adults with RA. It covers 4 domains: severity, distress, interference with daily living activities, and frequency and change during the previous week. It contains 15 items to form an aggregated score, the Global Fatigue Index (GFI) and a 16th item that does not contribute to the GFI. The global fatigue index ranges from 0 to 50 and higher scores reflect greater pain.[13]

The Fatigue Severity Scale (FSS) was developed to assess fatigue in multiple sclerosis and systemic lupus erythematosus, but it has been used in RA analysis. It covers physical, social or cognitive effects of fatigue, organized in 9 items to produce a global score. The items are scored 1 (strongly disagree) to 7 (strongly agree), summed and then averaged to produce a global score. Higher scores represent greater fatigue severity, distress, or interference.[14]

The Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ) was developed to assess overall experience and impact of fatigue, and its dimensions. It contains 20 items, providing a total fatigue score (0–70) and 4 subscales scores for physical (0–22), living with (0–21), cognitive (0–15) and emotional fatigue (0–12); higher scores reflect greater severity.[13]

The Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF-NRS) contains standardized numeric rating scales for measuring RA fatigue domains: Severity, Effect and Coping. Each scale scores 0–10, with higher scores reflecting greater severity and effect on life, and lower scores reflecting greater problems for coping with fatigue.[13]

The Fatigue Visual Analog Scale (VAS_F) is a unidimensional measure for severity or intensity of fatigue. It usually comprises a 0–10 cm horizontal line with a statement in each extremity. Higher scores represent greater severity or intensity of fatigue.[15] Regarding the VAS_F scale, the researchers assumed that the values below 2 would be considered as clinically irrelevant fatigue.

The vitality subscale of the SF36 questionnaire derives from a formula using 4 subitems ("a", "e", "g" and "i") of the 9th item of the instrument. Its score varies from 0 to 100 and, the lower the score the greater the fatigue.

The Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) was developed for measuring fatigue

Table 1 – Socioeconomic and demographic data of the patients with clinically relevant fatigue (VASf > 2, n = 57).

Variable	Mean (SD) or n (%)
Age	48.35 (±15)
Gender	
Male	6 (10.5%)
Female	51 (89.5%)
Ethnics	
White	17 (29.82%)
Pardo	32 (56.14%)
Negro	8 (14.04%)
Social class	
A (≥20 MW)	0 (0%)
B (10–20 MW)	1 (1.75%)
C (4–10 MW)	2 (3.5%)
D (2–4 MW)	10 (17.55%)
E (≤2 MW)	44 (77.2%)
Years of disease	4.92 (±3.8)
Marital status	
Single	10 (17.55%)
Married/common-law	29 (50.87%)
Divorced	9 (15.79%)
Widow	9 (15.79%)

SD, standard deviation; MW, Brazilian minimum wage.[16]

Table 2 – Independent variables scores of the patients with clinically relevant fatigue (VASf > 2, n = 57).

Variable	Mean/median[b]	SD/25–75%[b]
BMI	26.53	4.93
Years of disease	4.92	3.8
Morning stiffness (minutes)	15.00[b]	0.240[b]
ERS	9.5[b]	2.59[b]
CRP[a]	0.46[b]	0.01–16.00[b]
VAS pain	3.83	2.59
VAS patient	3.94	2.33
VAS provider	2.89	2.38
TJC	2.00[b]	0–28
SJC	0.00[b]	0–11[b]
SDAI	13.89	11.27
CDAI	12.89	10.87
HAQ	1.03	0.89
DAS28	2.9	1.41

BMI, Body Mass Index; ERS, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; VAS pain, pain Visual Analog Scale; VAS patient, patient global Visual Analog Scale; VAS provider, provider global Visual Analog Scale; TJC, Tender Joint Count; SJC, Swollen Joint Count; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; HAQ, Health Assessment Questionnaire; DAS28, Disease Activity Score with 28-joint counts.

[a] Data collected from 76 patients.

[b] Values presented in mean ± SD. Median (25–75%) or as specified in the variable.

Table 3 – Scores of the Fatigue Questionnaires used to assess fatigue in Brazilian RA Cohort patients.

Questionnaire	Mean	SD
SF36 vitality scale	55.93	±24.96
VAS fatigue	4.30	±2.95
POMS fatigue scale	7.95	±6.28
MAF-GFI	22.79	±13.38
FSS	4.11	±1.63
BRAF-MDQ	22.28	±16.33
BRAF-NRS fatigue	4.88	±3.02
FACIT-F	35.09	±11.01

SF36, Short-form 36; VAS, Visual Analog Scale; POMS, Profile of Mood States; MAF-GFI, Multidimensional Assessment of Fatigue-Global Fatigue Index; FSS, Fatigue Severity Scale; BRAF-MDQ, Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire; BRAF-NRS, Bristol Rheumatoid Arthritis Fatigue Numeric Rating Scale; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue Scale.

in oncology patients with anemia. The FACIT-F covers physical fatigue, functional fatigue, emotional fatigue and social consequences of fatigue. It contains 13 items with 5 responses from "Not at all" to "Very much". The items are scored 0–4, summed, multiplied by 13 and divided by the number of items actually answered. The global score ranges from 0 to 52 with higher scores reflecting less fatigue.[15]

The same researcher performed all fatigue assessments in order to optimize data collection and to clarify doubts about the items of each instrument.

Statistical analysis

Continuous data were expressed as mean and standard deviation, or 25th and 75th percentiles, according to the sample distribution. Categorical variables were recorded as percentages. Multiple bidirectional stepwise regression was applied due to the large number of potential explanatory variables and the lack of a defined theory to support a specific model of analysis. The analysis considered each fatigue score as dependent variable, and all the others collected as independent variables. The stepwise regression model was used to identify the highest R^2 for the tested model. Multicollinearity was considered present in the occurrence of tolerance $p < 0.1$ and VIF close to 1. For the multiple linear regression the assumptions of residues with normal behavior in the graphical representation Q–Q Plot and in the Shapiro–Wilk test were met. Statistical significance was set at 5% and all analyses were performed with SAS 9.3 software (SAS Institute Inc., North Carolina, USA).

Results

A total of 80 patients were assessed during the study, and 57 reported clinically relevant fatigue (VASf > 2), which represents a point prevalence of 71.25% (51 women [89.5%], mean age 48.35 ± 15 years, and mean disease duration of 4.92 ± 3.8 years). All socioeconomic and demographic data were showed in Table 1.[16]

SDAI and CDAI scores were 13.89 (11.27) and 12.89 (±10.87), respectively. The participants presented a mean HAQ score of 1.03 (±0.89), mean global pain (VAS_P) of 3.83 (±2.59) and mean DAS28 of 2.9 (±1.41). All others independent variables values were showed in Table 2. The specific scores of multiple instruments were presented in Table 3.

Regarding the predictive models, the explained variance for all instruments ranged from 21% to 56% (Table 4). The highest coefficient of determination (R^2) was 56% for SF-36 and the lowest (R^2 = 29%) for BRAF-NRS. All eight predictive models showed statistical significance. In the same way, in

Table 4 – Correlation analysis of the questionnaires used to assess fatigue in Brazilian RA Cohort patients.

Instrument	R^2 adjusted	Variable	*p*	*β*
SF36 vitality scale	0.56	HAQ	0.000	−0.542
		Age	0.001	0.325
		Morning stiffness	0.003	−0.299
		Manif. extra-joint	0.017	−0.217
VAS fatigue	0.54	HAQ	0.000	0.706
		VAS pain	0.000	0.697
		VAS patient	0.000	0.517
		Free T4	0.000	−0.434
		Aval. Subj. Cheers	0.001	0.370
		Age	0.007	−0.265
		TSH	0.047	−0.188
POMS fatigue scale	0.38	Age	0.000	−0.501
		HAQ	0.002	0.382
		Morning stiffness	0.036	0.245
MAF-GFI	0.45	HAQ	0.000	0.506
		Age	0.002	−0.335
		Free T4	0.002	−0.349
		TSH	0.037	−0.216
		Income	0.044	0.217
BRAF-MDQ	0.42	HAQ	0.000	0.630
		Age	0.000	−0.395
BRAF-NRS	0.29	HAQ	0.000	0.495
		Age	0.001	−0.405
FACIT-F	0.51	HAQ	0.000	−0.632
		Age	0.001	0.354
		ESR	0.024	−0.232
		BMI	0.032	0.202

HAQ, Health Assessment Questionnaire; VAS pain, pain Visual Analog Scale; VAS patient, patient global Visual Analog Scale; TSH, thyroid stimulating hormone; ESR, erythrocyte sedimentation rate; BMI, Body Mass Index.

all prediction models, the total of independent variables also were considered statistically significant. The HAQ was the only independent variable to predict fatigue on all instruments, and the second was age. There was no multicollinearity between the independent variables.

Discussion

This study was the first to assess fatigue in early RA patients, applying all fatigue instruments available in Portuguese, in an attempt to assess with sociodemographic and clinical variables would better predict fatigue.

Early RA affected predominantly women in our study, as expected, and is similar to other Brazilian demographic studies (varying from 86% to 92%).[6,17,18] Importantly, women seem to report somewhat more fatigue than men, which could have influenced the high prevalence of fatigue in our study.[19] Ethnicity differed (60% mixed race) probably because race was self-reported in our study. At the data collection, patients were

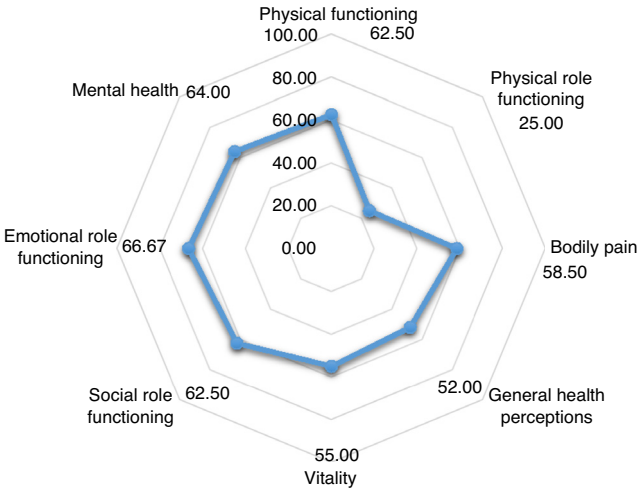

Fig. 1 – SF36 domains scores assessed in the Brazilian RA cohort patients.

asked to choose between the alternatives: black, white, pardo (mixed race), indigene or Asian.

This study identified that fatigue was better predict by disability (assessed with HAQ), independent of the multidimensional instrument, even in patients with low disability. Despite FACIT-F showing a negative value for its results there is a direct correlation with HAQ (the lower the FACIT-F score the higher the fatigue), as observed with the other instruments. This finding agrees with most of the studies analyzed, excluding those studies that did not assess this prediction. The HAQ mean values found in other studies varied from 0.44 to 1.1 also reflecting low disability.[6,8,20–30] Thus, it is important to assess fatigue even in patients with little or no functional limitation.

Observing the global assessment of the SF36 questionnaire, presented in Fig. 1, the low median score on the physical aspects assessed by the instrument corroborate with the association with disability found in our study.

Several studies found significant correlation between fatigue and disease activity (DAS28, TJC, SJC, SDAI, CDAI and/or ESR), and most of them assessed patients with moderate to high disease activity.[6,8,20,21,23,24] However, the absence disease activity in our study could have occurred because our sample presented disease activity predominantly in remission or low disease activity.

Fatigue is commonly associated with pain, mainly when assessing fatigue with the VASp[8,19,22–24,26,27,29,30] and although we found mean pain on VASp of 3.99 ± 2.66, which could be considered as mild to moderate pain, these variables showed no prediction.

There were no studies on BRAF-MDQ and BRAF-NRS in early RA to compare with our results.

Interestingly, our study shows that fatigue is also predicted by age – the younger the patient the higher the fatigue perception. This finding might be because the young are more active, performing multiple tasks in personal and professional life. Therefore, this may lead to an important economic and social impact. Nikolaus et al. conducted a qualitative study assessing patients' experience of fatigue and observed that

younger women with multiple daily roles were more susceptible to fatigue than men and older people.[30]

Several study limitations impede the generalization of our findings. As it happens in all cross-sectional studies, it is not possible to determine a cause/effect correlation between the variables; and the study of a specific cohort could be a selection bias. Psychosocial variables were not assessed for their correlation, which could affect the results of the study. In the same direction, despite the fact that 40% of the sample presented any comorbidity, it could be interpreted as a confounding variable and thus mediate the relationship between fatigue and disability, or influence the origin of fatigue.

Regarding other variables, such as hypothyroidism and fibromyalgia, the lack of homogeneity of the sample did not allow a significant statistical analysis, thus those were withdrawn as they could be potential confounding variables.

The adoption of different methods of analysis by other authors and the assessment of different variables in each study does not allow a reliable comparison between the available studies. Finally, other studies using different scales were not analyzed.

Longitudinal studies with larger samples could provide stronger evidence about cause/effect correlation between variables and provide a better comprehension on how sensitive to change the instruments actually are, as well as help in selecting the best instruments to assess fatigue.

Fatigue is a prevalent symptom even in early RA patients, thus, it should be considered as an outcome measure due to its impact on patients' lives. However, several simple and multidimensional instruments assess different domains and give different perspectives on how fatigue affects the patients. Identifying the best assessment instrument would result in a better comprehension of the clinical relationships of fatigue.

In conclusion, the prevalence of fatigue was high in early RA using different instruments. We identified that fatigue is better predicted by disability, independent of the multidimensional instrument, and age: the younger the patient the higher the fatigue perception.

Conflicts of interest

The authors declare no conflicts of interest.

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